Nephrotic Syndrome for the Internist

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KEYWORDS

• Glomerulonephritis • Nephrotic syndrome • Nephrotic syndrome/complications
• Nephrotic syndrome/pathophysiology • Nephrotic syndrome/management • Edema
• Hypoalbuminemia • Proteinuria

KEY POINTS

- Nephrotic syndrome (NS) is caused by a wide range of immunologic, infectious, malignant, and metabolic etiologies.
- NS presents with the constellation of edema, proteinuria of greater than 3 to 3.5 g per day, hypoalbuminemia, and hyperlipidemia.
- The complications of NS include edema, cardiovascular disease, kidney impairment, infections, and thrombosis.
- The initial serologic evaluation and supportive management of NS should start in the primary care office. Histologic diagnosis and directed therapy should be conducted by a nephrologist.

BACKGROUND

Nephrotic syndrome (NS) is a disorder of the kidney that is defined by the presence of greater than 3 to 3.5 g per day of proteinuria, which results in hypoalbuminemia, edema, and hyperlipidemia. NS occurs due to a disruption of the glomerular filtration barrier. This specialized barrier consists of three layers: fenestrated endothelial capillary cells, a basement membrane, and epithelial cells known as podocytes. This filtration barrier selectively filters fluid and solutes while preventing passage of protein and cells (**Fig. 1**). The structure is both size- and charge-selective, favoring passage of smaller or cationic molecules over larger or anionic molecules. The physiologic size of pores through the barrier creates the size selectivity.[1] The endothelial cells are covered by a negatively charged surface layer that creates the charge selectivity.[2] The consequence of this structure is that important proteins, such as albumin, immunoglobulins, and coagulation enzymes are preserved under normal conditions. NS occurs when sufficient

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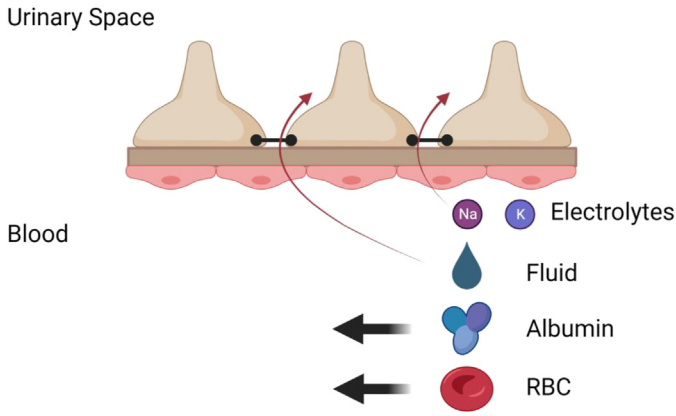

Fig. 1. Filtration barrier. The filtration barrier, which consists of three layers: fenestrated endothelial capillary cells, a basement membrane, and epithelial cells known as podocytes. As shown in this figure, this barrier selectively filters fluid and solutes and prevents the passage of protein and cells.

disruption occurs to various parts of filtration barrier, allowing for pathologic protein loss and leading to the complications described later in this article.

CAUSES OF NEPHROTIC SYNDROME

The primary classes of NS are minimal change disease, membranous nephropathy, and focal segmental glomerulosclerosis (FSGS). These classes are defined by the pattern of histologic lesions seen on a kidney biopsy. Each pattern of injury can be primary (or idiopathic), secondary to a systemic disease or exposure, or genetic, meaning that the underlying genetic abnormality has been identified. Outside of these primary causes are disease states that cause specific histologic lesions, such as amyloidosis and diabetic nephropathy. Membranoproliferative glomerulonephritis (MPGN) can present with an overlapping syndrome consisting of both nephritic and nephrotic features. **Table 1** demonstrates an overview of the common causes of NS.

COMPLICATIONS AND PATHOPHYSIOLOGY

Edema

Edema is the most defining feature of NS going back to even its earliest descriptions. Hippocrates described a state of generalized edema with the observation "when bubbles settle on the surface of the urine, it indicates a disease of the kidney and that the disease will be protracted."[3] The pathophysiology of edema in NS is primarily described by two primary theories: the "underfill" and "overfill" hypotheses.[4,5]

According to the "underfill" hypothesis, low serum albumin level caused by urinary protein losses is the primary driver of edema. Low serum albumin leads to leakage of fluid out of the vessels and into the interstitial space. This leads to low intravascular pressure and reduced renal perfusion, which stimulates the renin-angiotensin-aldosterone (RAAS) system and causes sodium retention and edema. Although physiologically appealing, this hypothesis does not seem to fully explain the edema observed in NS.[4,5]

The "overfill" hypothesis, in contrast, explains fluid retention in NS by direct changes to sodium handling by the kidneys.[4] Specifically, the changes seem to occur at the

Table 1
Classification of nephrotic syndrome by histology and common etiologies

Histology/Primary Disease	Secondary Causes (Examples)	Important Genetic Contributors
Minimal change	Drugs (NSAIDs, antibiotics, lithium, immune checkpoint inhibitors) Malignancies (hematologic) Infections (tuberculosis, HCV, Lyme disease) Allergies (bee stings, cat fur, fungi, poison ivy, ragweed pollen, dust)	
Membranous nephropathy	Lupus nephritis (class V) Drugs (NSAIDs, TNF-inhibitors, penicillamine) Infections (HBV, syphilis) Malignancies (solid tumors) Immunologic (immunoglobulin G4-related disease, graft versus host disease)	PLA2R antibody, THSD7, NELL1
FSGS	Glomerular hyperfiltration (obesity, unilateral kidney, low birth weight) Drugs (heroin, bisphosphonates, lithium, calcineurin inhibitors, anthracyclines) Infections (HIV, EBV, CMV, Parvovirus B19)	APOL1, NPHS1-2, ACTN4, TRPC6
Amyloidosis	Amyloid A amyloidosis, amyloid light chain amyloidosis	ALECT2, ATTR
MPGN	Viral infections (HBV, HCV) Autoimmune diseases (SLE, Sjogren's syndrome, rheumatoid arthritis) Cryoglobulinemia Bacterial infections (staphylococcus, streptococci, tuberculosis) Monoclonal gammopathies Fungal and parasitic infections Complement-mediated MPGN	Genetic complement abnormalities

Abbreviations: ACTN4, actinin alpha 4; ALECT2, amyloid leukocyte chemotactic factor 2; Amyloid, transthyretin; APOL1, apolipoprotein L1; CMV, cytomegalovirus; EBV, Epstein–Barr virus; NELL1, neural EGFL-like 1; NPHS1, nephrin; NPHS2, podocin; NSAIDs, nonsteroidal anti-inflammatory drugs; PLA2R, phospholipase A2 receptor; SLE, systemic lupus erythematosus. THSD7; thrombospondin, type-1 domain-containing 7A; TNF, tumor necrosis factor; TRPC6, transient receptor potential cation channel subfamily C member 6.

Data from Refs.[36–38,40–42]

level of the epithelial sodium channel (ENaC) in the nephron. This channel, when inserted into the tubular epithelium of the cortical collecting duct, allows for sodium reabsorption back into circulation. According to the "overfill" hypothesis, a primary increase in ENaC activity drives increased sodium retention. This hypothesis has been supported by rat models demonstrating increased ENaC channel expression, which seems to be triggered by the presence of proteins in the urine.[6–10] In support of this hypothesis, there are rat models and limited human data demonstrating the resolution of sodium retention in response to ENaC blockade.[11,12] In addition to primary sodium retention, there are neurohormonal changes in vasopressin and aldosterone that contribute to fluid retention in NS.[4]

Hypercoagulability

Arterial and venous thrombosis represents an important complication of NS. The underlying histopathology of NS is a significant determinant of thrombotic risk, with membranous nephropathy carrying the highest risk of thromboembolic events.[13–15] Of note, NS carries a particularly elevated risk of renal vein thrombosis, with an overall 37% prevalence identified across studies of membranous nephropathy and 28% across other histopathologies.[13] Other types of thrombosis are also observed at increased rates, including arterial clots, deep vein thrombosis, and pulmonary emboli.[14,16] The pathophysiology of hypercoagulability in NS has classically been explained by urinary protein losses that alter the balance of prothrombotic to antithrombotic proteins. Specifically, urinary loss of important anticoagulant and fibrinolytic proteins, such as antithrombin and plasminogen, contributes to dysregulation of the coagulation cascade.[16–18] Another apparent cause of hypercoagulability is increased hepatic synthesis of procoagulant factors, such as factors V and VIII.[16] It is hypothesized that hypoalbuminemia triggers the increased synthesis of these proteins by the liver with a low urinary loss due to size. The particularly high risk for renal vein thrombosis may relate to local clot formation promoted by glomerular inflammation and to glomerular hemodynamic changes in NS.[13,19]

The thrombotic risk in NS correlates with the degree of hypoalbuminemia.[14,20] This correlation reflects the urinary protein losses of albumin and anti-thrombotic proteins as well as the fact that albumin is an acute phase reactant that drops in inflammatory states. The increase in thrombotic risk seen at low serum albumin levels supports anticoagulation recommendations for NS, as discussed under the management section.

Infection

Infection risk in NS is best described in the pediatric population, in whom infections are a leading cause of morbidity and mortality. Among children, invasive bacterial infections from encapsulated organisms and gram-negative enteric organisms are the most common serious infections observed.[21–23] The infection risk is multifactorial, related to both the underlying pathophysiology and the use of immune suppressive treatments. Urinary losses of immune proteins such as immunoglobulin G and reduced function of immune cells (T cells, phagocytes) are contributors to decreased immunity.[24,25] Mainstays of treatment include steroids and cytotoxic medications which endanger patients to serious infections.

Hyperlipidemia and Cardiovascular Risks

Hyperlipidemia is a hallmark laboratory finding of NS. It has classically been explained by increased hepatic synthesis of lipoproteins triggered by hypoalbuminemia.[26] There is also evidence for decreased clearance of lipoproteins relating to changes in catabolism.[26] Hyperlipidemia contributes to, though likely does not fully explain, increased

cardiovascular risk observed across NS. A population-based study of 907 patients with primary NS with matched healthy adults showed a significantly elevated risk of cardiovascular events.[27] This study demonstrated an adjusted hazard ratio of 2.58 (95% CI 1.89–3.52) for acute coronary syndrome and an adjusted hazard ratio of 3.01 (95% CI 2.16–4.19) for heart failure.[27] The increased cardiovascular risk likely reflects effects from hyperlipidemia, hypercoagulability, generalized inflammation, and kidney injury.

Kidney Injury

The spectrum of kidney impairment seen in NS is broad, encompassing acute kidney injury (AKI), chronic kidney disease (CKD), and progression to end-stage kidney disease (ESKD). Etiologies for AKI include abrupt changes in renal perfusion, acute interstitial nephritis from exposure to antibiotics and diuretics, acute tubular necrosis, and rapidly progressive glomerular injury.[28] CKD can develop from recurrent AKI, treatments such as calcineurin inhibitors (CNIs), and primary glomerular injury. Rates of progression to ESKD are broadly variable based on the underlying histopathology and treatment course. The risk of progression to ESKD is highest among patients with FSGS, followed by membranous nephropathy and then minimal change disease.[27]

MANAGEMENT

Often the diagnosis of NS occurs in the primary care setting. Once diagnosed, the patient should be evaluated by a nephrologist for further management. A kidney biopsy is commonly required to diagnose the cause of NS and to guide disease-specific therapy. For this review, the authors divide the management of NS into supportive and disease-specific therapy. The main goal of treatment is to get the disease under remission and avoid progression to ESKD. This involves the use of immunosuppressive agents directed by a nephrologist. However, supportive treatment should be started by the primary care physician (PCP). It is preferable to avoid immunosuppression therapy before evaluation as this could affect the diagnosis and cause unnecessary toxicity.[29]

Initial Evaluation

The evaluation of a patient with NS requires a thorough history and physical examination to assess for potential causes. It is essential to quantify the degree of proteinuria. This can be done by obtaining a 24-hour urine collection for protein quantification or a spot protein to creatinine ratio.[30] The assessment of the estimated glomerular filtration rate (eGFR) using the CKD epidemiology collaboration eGFR creatinine equation (CKD-epidemiology [EPI]) is preferred in adults.[30] The authors recommend the CKD-EPI without the race modifier equation. An evaluation of serum albumin level and lipid profile is also important. Serologic workup can be initiated by the PCP, based on the differential diagnosis (**Table 2**).

Kidney biopsy remains the gold standard for diagnosis, as it will also guide therapy and provide prognostic information. It is usually preferable to get a kidney biopsy before starting management; however, preemptive treatment can be considered in specific clinical conditions.[30]

Supportive Management

Edema

Edema represents a huge symptomatic burden for this patient population. It causes functional limitations and results in complications, as previously discussed. Loop

Table 2
Diagnostic evaluation in patients with nephrotic syndrome

Baseline assessment	History (exposure to medications and toxins, risk factors for infections, history of diabetes or other systemic disease and family history, and so forth) 24-h urine protein to creatinine and/or random urine to protein to creatinine ratio Urinalysis with microscopy Basic metabolic panel Serum albumin level Lipid panel Hemoglobin A1C
FSGS	Genetic testing (including APOL1) Infectious workup: HIV, CMV, Parvovirus b19, EBV, HCV, SARS-COV2 History of drug use: mTOR inhibitors, CNIs, heroin, lithium, interferon, NSAIDs, anabolic steroids Kidney biopsy
Minimal change disease	History of drug use: NSAIDs Kidney biopsy
Membranous nephropathy	Serologic workup: anti-PLA2R and anti-THSD7A Screening for malignancy (age appropriate) ANA Infectious workup: HBV, HCV, HIV, and treponemal infection History of drug use: NSAIDs, penicillamine. Kidney biopsy
Amyloidosis/Multiple myeloma	Serum electrophoresis with immune fixation electrophoresis and free light chain ratio.

Abbreviations: ANA, antinuclear antibody; mTOR, mammalian target of rapamycin; SARS-COV2, severe acute respiratory syndrome coronavirus 2.
Data from Refs.[36–38,40–42]

diuretics are the preferred agents to treat edema per the most recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines 2021.[30] There is no evidence to guide the selection of diuretics and the starting dose. The authors prefer longer acting diuretics for the treatment of edema. Intravenous (IV) administration is recommended in cases of severe or refractory edema. Response to diuretics is usually measured based on the change in daily weight and urine output. Based on expert opinion, the goal weight loss is 2 to 4 pounds per day to avoid complications.[31] The dose of loop diuretics should be titrated up until desired diuretic response is achieved. In instances when loop diuretics are not sufficient, a thiazide or thiazide-like diuretic can be used to augment diuresis.[31]

Achieving an effective diuresis regimen can be challenging due to the pharmacodynamics of these medications. Loop diuretics act on the luminal side of the tubular epithelium. To have an appropriate effect, diuretics need to reach an adequate concentration inside the tubules. This can be particularly challenging in patients with NS due to diffusion of diuretic into the extracellular space, reduced concentration inside the tubules, and binding of loop diuretics to albumin in the tubular fluid.[31] Also, most patients have some degree of gut edema that limits absorption, hence the preference for IV administration or longer-acting loop diuretics with increased bioavailability.[32] In patients with severe hypoalbuminemia (<2 g/dL), the combination of albumin infusions and loop diuretics may enhance diuresis and is reasonable to consider.[31]

Lifestyle changes

Patients with proteinuria and kidney disease should be on a sodium restricted diet (<1500–2000 mg/d). The benefit of protein restriction is currently debated. Protein restriction to less than 0.8 g/kg/d does not offer any additional advantages.[29,30] KDIGO 2021 guidelines suggest that based on the kidney function and degree of proteinuria, dietary protein restriction should be considered up to 0.8 g/kg/d, with 1 g of daily protein added per gram of urinary loss. Dietary modifications and regular physical activity are recommended to normalize body mass index (BMI), reduce central obesity, and decrease cardiovascular risk factors.[30]

Hypertension

Goal systolic blood pressure (BP) is less than 120 mm Hg with angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEis) as first choice.[30] ARBs and ACEi should be increased to the maximal tolerated dose. Adding a mineralocorticoid receptor antagonist has been shown to offer further improvement in lowering BP and proteinuria, although dual-RAAS blockade is avoided for control of proteinuria alone due to the risk of hyperkalemia. If hyperkalemia develops while on RAAS blockade, a potassium-wasting diuretic can be used as tolerated.[30] As previously discussed, loop diuretics should be prescribed if volume overload is present.

Proteinuria

Reducing the amount of proteinuria has been shown to reduce the progression of kidney disease. ARB and ACEi are the mainstay of treatment. These medications should be initiated even in the absence of hypertension to the maximum tolerated doses.[30]

Most recently, sodium–glucose cotransporter-2 inhibitors (SGLT2is) have gained momentum in the management of nephrosis. It is well known that SGLT2is are beneficial in treating patients with diabetes and proteinuria as well as in delaying progression of kidney disease in patient with and without proteinuria. In a comprehensive review, Zeynegpul and colleagues reviewed nine clinical studies evaluating the use of SGLT2i in a total of 592 patients with nephrotic range proteinuria.[33] Findings support a possible beneficial effect in lowering proteinuria and delaying progression of CKD in patients with nephrotic range proteinuria. However, currently, SGLT2is are not recommended for treatment of proteinuria in NS outside of diabetic nephropathy.

Anticoagulation. The risk for thromboembolic events in patients with NS is well established; however, there is no clear evidence to guide the use of prophylactic anticoagulation in this patient population.[34] Prophylactic anticoagulation should be considered if serum albumin is less than 2.0 to 2.5 g/dL with additional risk factors for thrombosis (proteinuria >10 g, BMI >35, genetic predisposition to thromboembolic events, heart failure III–IV, recent major surgery, or prolonged immobilization).[34] Prophylactic anticoagulation should be used when the risk for a thromboembolic event exceeds the estimated risk of bleeding.[30] Aspirin can be considered in patients with high risk for thromboembolism who are not a candidate for anticoagulation due to bleeding risk.[34]

The decision to start or hold prophylactic anticoagulation should be made in collaboration with a specialist. Patients should not start anticoagulation before evaluation by a nephrologist as this could delay biopsy.[30,34] However, in patients presenting with a thromboembolic event, initiation of treatment dose anticoagulation should not be delayed.[30]

Hyperlipidemia

Lipid levels should be monitored in patients with NS. Treatment of dyslipidemia should be initiated in patients with NS, particularly in those with additional cardiovascular risk

factors. Statins are the first-line pharmacologic agents to be used along with lifestyle modifications. Non-statin medications can be added if statins are not tolerated or if goal is not achieved with maximally tolerated statin doses.[30] An additional benefit of statin therapy is their anti-proteinuric effect.[35]

Infections

Patients with impaired immunity should be up to date with vaccinations. Practice guidelines recommend pneumococcal, herpes zoster, and influenza vaccination for patients with NS.[30] Screening for syphilis, hepatitis C virus (HCV), hepatitis B virus (HBV), human immunodeficiency virus (HIV), and tuberculosis is suggested in clinically appropriate patients. Pneumocystis jiroveci pneumonia prophylaxis should be prescribed for patients receiving high-dose steroids and other immunosuppressive therapy.[30]

DISEASE-SPECIFIC MANAGEMENT

Disease-specific and immunosuppressive therapy should be deferred to a nephrologist. Treatment varies with the underlying histopathology and etiology. In all types of NS, secondary causes are managed by treating the underlying disease or removing the offending agent. Here, the authors briefly review possible therapeutic approaches.

Focal Segmental Glomerulosclerosis

Patients with primary FSGS and in some cases genetic FSGS require immunosuppressive therapy.[36] High-dose steroids remain the first line of treatment (Grade 1D per KDIGO 2021).[29] In patients not responding to or intolerant to steroids, a trial of CNIs is recommended (Grade 1C).[30,36] RAAS inhibition is the cornerstone of treatment to avoid progression of CKD. Thiazide diuretics and a low sodium diet may potentiate the antiproteinuric effect of RAAS inhibition.[36]

Minimal Change Disease

The management of minimal change disease in adults is composed of RAAS blockade, low sodium intake, and glucocorticoids. The optimal steroid regimen is not well-defined. High-dose glucocorticoids should not be given for more than 16 weeks. Tapering should start 2 weeks after remission is achieved.[30,37] If there are contraindications to glucocorticoids or if the patient has relapsing disease, further immunosuppressive treatment options include cyclophosphamide, CNI, mycophenolate, and rituximab.[30,37]

Membranous Nephropathy

Primary membranous nephropathy patients should be risk-stratified before receiving immunosuppressive therapy. Low-risk patients are treated with symptom management and risk modification only. Patients at moderate risk of kidney disease progression can be managed conservatively or with immunosuppression (rituximab or CNIs and glucocorticoids). For patients at high risk, immunosuppressive therapy with rituximab, cyclophosphamide and steroids, or CNIs and rituximab is recommended. Patients at very high risk for progression to ESKD are managed primarily with cyclophosphamide and steroids.[30]

Amyloid

The management of amyloidosis with renal involvement is multidisciplinary, involving hematology/oncology and nephrology. RAAS blockade should be used cautiously in patients with amyloid light chain (AL) cardiac amyloidosis due to the risk of hypotension.

Disease-targeted therapy should be directed by specialists and will vary depending on the type of amyloid.[38]

Diabetic Nephropathy

Diabetes is one of the leading causes of NS. In addition to diabetic control and lifestyle modifications, there are medications that carry significant kidney and cardiac protective effects and that decrease proteinuria in patients with diabetic nephropathy.

Patients with diabetes and proteinuria should be initiated on RAAS blockade, even in the absence of hypertension, titrated up to the highest tolerated dose. The kidney function and potassium level should be monitored 2 to 4 weeks after initiation or dose changes.[39] Increase in the serum creatinine is expected and RAAS blockade should not be stopped unless it rises by greater than 30% and there are no other causes of AKI.[39] In the case of hyperkalemia, a low-potassium diet and potassium binders can be considered before the discontinuation of the medication. Women of reproductive age should be counseled on the teratogenic effects of RAAS blockade and initiated on contraception if pregnancy is not desired.

As previously discussed, the kidney and cardiovascular protective effects of SGLT2i in patients with kidney disease and proteinuria are well-known. SGLT2is are particularly important tools in the management of type 2 diabetic nephropathy. SGLT2i should be considered in all patients with eGFR greater than 20 mL/min/1.73 m.[2] A drop in eGFR is expected and should not be a reason to stop the medication. Given the association of these medications with normoglycemic ketoacidosis, it is reasonable to hold them during times of high stress, prolonged fasting, or critical medical illness.[39]

SUMMARY

NS is the common presentation of a wide group of diseases that cause proteinuria, hypoalbuminemia, and edema. The diagnosis of the exact cause and disease-specific treatment requires early evaluation by a nephrologist. The internist plays a critical role in detecting early workup and general management of the disease.

CLINICS CARE POINTS

- On recognition of nephrotic syndrome, the patient should be promptly referred to nephrology, but evaluation and supportive management can begin in the primary care office.
- The initial evaluation of nephrotic syndrome should include a thorough medication review, quantification of urinary protein losses, and measurement of kidney function and lipid levels.
- The initial diagnostic evaluation can include infectious serologies, age-appropriate cancer screening, and specific antibody testing as guided by the history and physical examination.
- Supportive management includes diuresis, vaccination, blood pressure control, management of cardiovascular risk factors, suppression of proteinuria, and in some cases anticoagulation.
- Histologic diagnosis and immune suppressive therapy should be directed by a nephrologist.

DISCLOSURE

K. Jain has served as the site PI for Visterra IgA phase 2 trial and Kaneka LDL Apheresis study. Remaining authors have no other disclosures.

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